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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,545	04/05/2006	Enrico Anthony Antonini	1679 WO/US	4059

7590 11/21/2008

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EXAMINER	
CHANDRAKUMAR, NIZAL S	
ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
11/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,545	ANTONINI, ENRICO ANTHONY	
	Examiner	Art Unit	
	NIZAL S. CHANDRAKUMAR	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 09/25/2008 has been entered.

Status of Claims:

Claims 1, 3-25 are pending.

Applicant's amendments to claims were noted.

Response to Applicants Remarks filed 09/25/2008 is found after the section under **Double Patenting.**

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

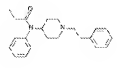
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

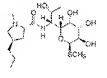
Claims 1, 3-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hofstadter (1982, US 4,317,903).

Instant claims

The instant claims drawn to an industrial process for the purification of fentanyl using reverse phase high performance liquid chromatography. The structure of fentanyl is shown below.



Fentanyl



Lincomycin

Prior Art

Hofstetter teaches an industrial process for the purification of Lincomycin using reverse phase high performance liquid chromatography. Lincomycin (structure shown above), like fentanyl, morphine, hydrocodone and naltrexone is a tertiary amine and is

anticipated to have similar chromatographic properties. Hofstetter teaches chromatographic purification using silanized silica stationary support, including all the details such as loading ratio, solvent etc.

The difference

Hofstetter does not teach the purification of fentanyl by reverse phase high performance liquid chromatography. Hofstetter does not teach all the broadly stated limitations of the instant claims. The instant claims are drawn to known methods of purifying compounds by optimization within prior art teachings and conditions or through routine experimentation.

One skilled in the art of process research developing alternate methods of purification of fentanyl would be motivated to modify the process of Hofstetter for the purification of fentanyl because Hofstetter teaches the conditions necessary of purification of a similar compound with similar chromatographic properties. Substituting fentanyl for lincomycin in the process of Hofstetter would require routine optimization of conditions, but this would be within the capabilities of one skilled in the art. As such one of ordinary skill in the art of organic process research, by routine optimization of existing processes of Hofstetter, by altering by mere substitution of one element for another known in the art, would arrive at the limitations of instant claims. MPEP states that "W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Prior art not relied upon:

Reversed-phase high-performance *liquid chromatographic* separation of fentanyl homologs and analogs. An optimized isocratic chromatographic system utilizing absorbance rationing. Lurie, Ira S.; Allen, Andrew C.; Issaq, Haleem J. Journal of Liquid Chromatography (1984), 7(3), 463-73.

Reversed-phase high-performance *liquid chromatographic separation* of fentanyl homologs and analogs. II. Variables affecting hydrophobic group contribution Lurie, I. S.; Allen, A. C.
Journal of Chromatography (1984), 292(2), 283-94

Simultaneous determination of fentanyl and midazolam using high-performance *liquid chromatography* with ultraviolet detection. Portier, E. J. G.; de Blok, K.; Butter, J. J.; van Boxtel, C. J.
Journal of Chromatography, B: Biomedical Sciences and Applications (1999), 723(1 + 2), 313-318.

Methods for the large scale synthesis of psoralen furna-side monoadducts and diadduccts. Hearst et. al.
Proceedings of the National Academy of Sciences, USA. 1992, 89, 4514-4518.

Preparative separation of steroids by reverse phase HPLC. Sergio et al. EP 1398320 A1

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/501353, 11/576059,11/916036. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of all the claims relates to processes of reverse phase high performance liquid chromatographic purification methods for samples that are anticipated to have similar

chromatographic behavior. As such routine method of process described in application would provide methods for the purification of other similar compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claim is allowed.

Response to Applicants Remarks:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Previously presented rejection of claims 1, 3-25 is maintained for reasons of record.

Applicant's remarks as well as the Affidavit filed 09/25/2008 were fully considered but are not persuasive. Applicant's arguments are based on reasons centering on the distinctness of the product being purified. Further, applicant states that the cited reference does not teach the limitations of the instant claims and the cited art teaches away from the recited claim limitations. Applicant also state that 'the office has used hindsight reconstruction' using Applicants invention as a blueprint.

Applicants Remarks and Affidavit focus on the difference between the cited and the instant claims, even though, as stated in the previous office action filed 07/17/2008, (page 3, line 1), the cited prior art is only an Example of methods of the hplc purification technology in the chemical art at the time of the instant application. *In this context Applicant's attention is directed to additional references listed in this office action and previous office action.* It is routine practice in the art of purification of polar compounds by high performance chromatography to adjust and modify by iterations, loading ratios, solvents etc..which are process parameters, recited as instant claim limitations. Such optimization of routine methods is part of the capabilities of a person of ordinary skilled in the art.

A search for the terms 'hplc industrial' in Google results in over 1,280,000 hits. One of example of these is "HPLC : practical and industrial applications by Joel Swadesh". The following is found in the Editorial Reviews for this guide to hplc: Product specifications, regulatory constraints, and tight production schedules impose considerable pressures on separation scientists in industry. The first edition of HPLC: Practical and Industrial Applications helped eliminate the need for extensive library or laboratory research when confronting a problem, an unfamiliar technique, or work in a new area. Its plain language, comprehensive coverage of separation topics, and practical organization made it an accessible and convenient reference manual for anyone working in or just entering the field. Since its publication in 1997, however, much has changed. The areas of mass spectroscopy, electrophoretic separations, and ultra-micro separations have blossomed, focus on quality control has intensified, and

the literature has grown significantly. The Second Edition incorporates all of these changes and more. It is now fully current, with chapter supplements that include updated references and discussions of techniques. This book examines analytical HPLC as it is actually used in industry. Whether you are just entering industry, switching from one industry to another, or simply enjoy understanding how things are made, HPLC: Practical and Industrial Applications will help you solve problems and get up to speed in new areas quickly, comfortably, and with a genuine sense of mastery.

Double Patenting: Previously presented rejections are maintained for reasons of record. Applicants would address the double patenting rejections if the listed applications issue as patents before the application at hand.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

/D. Margaret Seaman/
Primary Examiner, Art Unit 1625